Synthesis of 3,4-Dihydro-2(1*H*)-pyridinone Derivatives

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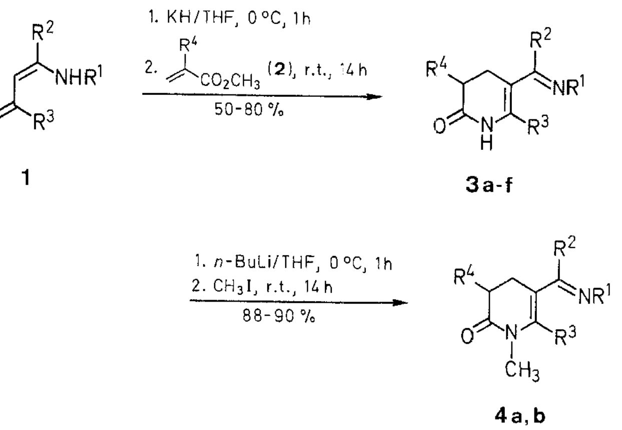
The synthesis of 3,4-dihydro-2(1*H*)-pyridinone derivatives **3** and **4** from 4-amino-1-azabutadienes **1** and methyl acrylate and methacrylate is described.

The 2- and 4-pyridone moiety is found in a great number of naturally occurring compounds, e.g. alkaloids and other products having physiological properties.[1] Regarding the 3,4-dihydro-2(1*H*)-pyridinone ring, the most general routes for its synthesis are the reaction of enamines with α,β-unsaturated nitriles[2] and the reaction of 5-oxopentanoic acid derivatives with ammonia;[3] less general methods include the reaction of ester enolates[4] and 2,4-diphenyloxazol-5(1*H*)-one[5] with azadienes.

In previous papers we have reported the ability of 4-amino-1-azabutadienes to form regioselectively five-, six- and eight-membered heterocycles.[6] We wish to report here a versatile synthesis of dihydropyridone derivatives by reaction of 4-amino-1-azabutadienes with methyl acrylate and methacrylate.

The lithium metallated derivatives of azadienes **1** were reported to undergo *C*-alkylation with alkyl halides,[7] although, acrylic acid esters did not react. We now report that, when potassium is used as the counterion, a smooth reaction is observed; thus treatment of **1** with potassium hydride (tetrahydrofuran, 0 °C) followed by addition of **2** results in the formation of heterocycles **3** in good to excellent yields (see Table 1, Scheme A).



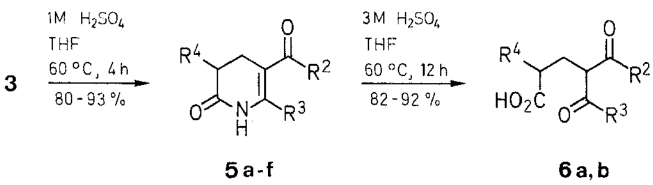
3	R^1	R^2	R^3	R^4
a	C_6H_5	C_6H_5	C_6H_5	H
b	C_6H_5	C_6H_5	p-$CH_3C_6H_4$	H
c	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	H
d	p-$CH_3C_6H_4$	C_6H_5	c-C_6H_{11}	H
e	c-C_6H_{11}	H	p-$CH_3C_6H_4$	H
f	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	CH_3

4	R^1	R^2	R^3	R^4
a	C_6H_5	C_6H_5	C_6H_5	H
b	C_6H_5	C_6H_5	p-$CH_3C_6H_4$	H

Scheme A

Michael addition of the β-enamine carbon followed by intramolecular ring closure accounts for the formation of **3**. The structure **3** was deduced from its combustion analyses and spectroscopic data. For instance, the ^{13}C-NMR spectrum of **3a** ($R^1 = R^2 = R^3 = C_6H_5$; $R^4 = H$) shows signals at $\delta = 171.4$ (C=O), 166.9 (C-6), 110.2 (C-5), 29.1 and 26.0 (C-3 and C-4).

Methylation of **3** (RLi, CH_3I) took place exclusively at the ring nitrogen to give compounds **4** (Table 1, Scheme A), in agreement with the published findings for this type of process.[8]



5	R^2	R^3	R^4
a	C_6H_5	C_6H_5	H
b	C_6H_5	p-$CH_3C_6H_4$	H
d	C_6H_5	c-C_6H_{11}	H
e	H	p-$CH_3C_6H_4$	H
f	C_6H_5	C_6H_5	CH_3

6	R^2	R^3	R^4
a	C_6H_5	C_6H_5	H
b	C_6H_5	p-$CH_3C_6H_4$	H

Scheme B

Controlled acid hydrolysis of **3** (1 M sulfuric acid, 60 °C, 1 equivalent) gave rise to imine cleavage to yield 5-acyl-3,4-dihydro-2(1*H*)-pyridinone derivatives **5**. More vigorous hydrolysis (3 M sulfuric acid, 60 °C, excess) afforded β-dicarbonyl compounds **6** (Table 2, Scheme **B**), which are not available by direct alkylation of their precursors 1,3-diketones.[7] The ^{13}C-NMR spectrum of **6a** ($R^2 = R^3 = C_6H_5$, $R^4 = H$) shows signals at $\delta = 195.7$ (C=O), 172.7 (CO_2H), 55.0 (CH), 31.3 and 23.9 (CH_2CH_2).

Table 1. 5-Imidoyl-3,4-dihydro-2(1*H*)-pyridinones **3** and **4** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ	MS m/z (M^+)
3a	82	193–195[c]	$C_{24}H_{20}N_2O$ (352.4)	2.52 (s, 4H, 2 × CH_2); 6.23–8.04 (m, 16H, 15H_{arom} + NH)	26.0, 29.1, 110.2, 119.5, 123.2, 127.2, 128.3, 128.4, 129.0, 130.6, 134.1, 137.2, 138.2, 150.9, 166.9, 171.4	352
3b	81	178–180[c]	$C_{25}H_{22}N_2O$ (366.5)	2.24 (s, 3H, CH_3); 2.45 (s, 4H, 2 × CH_2); 6.23–8.04 (m, 15H)	20.9, 25.8, 29.0, 109.4, 119.4, 123.0, 126.9, 128.0, 128.2, 128.3, 128.7, 130.4, 131.1, 137.2, 138.1, 138.8, 151.0, 167.0, 171.2	366
3c	76	196–198[c]	$C_{25}H_{22}N_2O$ (366.5)	2.25 (s, 3H, CH_3); 2.45 (s, 4H, 2 × CH_2); 6.17–7.96 (m, 14H_{arom})	18.1 (q), 23.3 (t), 26.5 (t), 107.7 (s), 116.9 (d), 124.6–131.6, 134.6 (s), 135.8 (s), 145.9 (s), 164.1 (s), 168.6 (s)	366
3d	70	215–218[c]	$C_{25}H_{28}N_2O$ (372.5)	0.83–2.10 (m, 11H, *c*-C_6H_{11}); 2.32 (m, 7H); 6.62–7.96 (m, 10H)	20.8, 25.4, 25.8, 26.2, 29.2, 29.6, 39.6, 107.4, 120.1, 128.3–133.4, 138.9, 139.3, 148.8, 167.3, 171.5	372
3e	74	149–151[c]	$C_{19}H_{24}N_2O$ (296.4)	0.7–1.93 (m, 10H); 2.32 (m, 7H); 7.25 (s, 4H_{arom}); 7.88 (s, 1H)	20.4 (t), 21.0 (q), 24.9 (t), 25.2 (t), 29.9 (t), 34.2 (t), 69.3 (d), 113.5 (s), 128.7 (d), 129.1 (d), 130.0 (s), 139.3 (s), 141.9 (s), 155.2 (d), 171.4 (s)	296
3f	47	122–124[c]	$C_{26}H_{24}N_2O$ (380.5)	1.22 (d, 3H, $J = 6.5$; CH_3); 2.1–2.7 (m, 6H); 6.15–8.04 (m, 15H)	14.3, 20.1, 33.1, 33.9, 110.1, 119.3, 126.9, 127.3–132.9, 136.9, 138.3, 148.0, 166.2, 173.6	380
4a	88	oil[d]	$C_{25}H_{22}N_2O$ (366.5)	2.36 (m, 4H, 2 × CH_2); 2.60 (s, 3H, NCH_3); 6.1–7.8 (m, 15H_{arom})	26.5 (t), 30.9 (t), 33.3 (q), 116.4 (s), 121.1 (d), 124.4 (d), 129.1–134.6, 139.6 (s), 142.6 (s), 151.9 (s), 167.7 (s), 171.9 (s)	366
4b	90	138–140[c]	$C_{26}H_{24}N_2O$ (380.5)	2.17 (s, 3H, CH_3); 2.37 (m, 4H, 2 × CH_2); 2.60 (s, 3H, NCH_3); 6.15–7.85 (m, 14H_{arom})	20.0 (q), 24.2 (t), 29.0 (t), 31.0 (q), 114.0 (s), 119.6 (d), 122.5 (d), 127.0–130.4, 138.2 (s), 141.0 (s), 150.6 (s), 166.5 (s), 170.6 (s)	380

[a] Yield of isolated purified product.

[b] Satisfactory microanalyses obtained: C ± 0.25, H ± 0.15, N ± 0.15.

[c] Recrystallized from hexane/chloroform.

[d] bp: 155–160 °C/0.001 Torr.

Table 2. 5-Acyl-3,4-dihydro-2(1*H*)-pyridinones **5** and 4,4-Diaroylbutanoic Acids **6** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ	MS m/z (M^+)
5a	85	228–230[c]	$C_{18}H_{15}NO_2$ (277.3)	2.80 (m, 4H, 2 × CH_2); 6.98–7.65 (m, 11H)	24.0, 30.3, 114.0, 127.5, 128.0, 128.3, 129.7, 131.5, 136.0, 138.0, 171.5, 198.5	277
5b	84	170–172[c]	$C_{19}H_{17}NO_2$ (291.3)	2.13 (s, 3H, CH_3); 2.76 (m, 4H, 2 × CH_2); 6.80–7.66 (m, 9H_{arom}); 7.80 (s, NH)	20.8 (q), 24.5 (t), 30.5 (t), 113.6 (s), 127.5 (d), 128.4 (d), 128.6 (d), 130.9 (s), 131.3 (d), 138.0 (s), 139.6 (s), 144.1 (s), 171.7 (s), 197.2 (s)	291
5d	80	153–155[c]	$C_{18}H_{21}NO_2$ (283.4)	0.78–1.89 (m, 11H); 2.48 (m, 4H, 2 × CH_2); 6.98–7.81 (m, 5H)	23.9, 25.2, 25.7, 29.7, 30.4, 39.1, 111.9, 128.2, 132.1, 139.3, 148.9, 172.2, 197.0	283
5e	93	195–197[c]	$C_{13}H_{13}NO_2$ (215.2)	2.28 (s, 3H, CH_3); 2.40 (m, 4H, 2 × CH_2); 7.17 (s, 4H); 9.26 (s, 1H)	18.0, 21.2, 29.9, 115.3, 127.9, 129.1, 129.4, 141.4, 154.2, 171.3, 189.8	215
5f	87	193–195[d]	$C_{19}H_{17}NO_2$ (291.3)	1.27 (d, 3H, $J = 6.5$, CH_3); 2.68 (m, 3H); 6.94–7.55 (m, 10H); 7.31 (s, NH)	14.0, 31.9, 34.1, 113.5, 128.6, 129.0, 129.2, 129.6, 130.0, 131.7, 134.0, 138.1, 143.8, 174.1, 197.3	291
6a	92	116–118[d]	$C_{18}H_{16}O_4$ (296.3)	2.40 (m, 4H, 2 × CH_2); 5.36 (t, 1H, $J = 6.2$, CH); 7.13–8.02 (m, 10H); 9.73 (s, 1H, CO_2H)	23.9 (t), 31.3 (t), 55.0 (d), 128.5 (d), 128.8 (d), 133.5 (d), 135.6 (s), 172.7 (s), 195.7 (s)	296
6b	82	oil[e]	$C_{19}H_{18}O_4$ (310.3)	2.28 (s, 3H, CH_3); 2.48 (m, 4H, 2 × CH_2); 5.36 (t, 1H, $J = 6.2$, CH); 7.01–8.06 (m, 9H); 9.97 (s, 1H, CO_2H)	22.3 (q), 24.8 (t), 32.2 (t), 55.7 (d), 128.5–129.3, 133.6 (d), 133.9 (s), 136.6 (s), 145.4 (s), 179.3 (s), 196.4 (s), 196.8 (s)	310

[a] Yield of isolated purified product.

[b] Satisfactory microanalyses obtained: C ± 0.30, N ± 0.20, N ± 0.30.

[c] Recrystallized from hexane/chloroform.

[d] Recrystallized from diethyl ether.

[e] bp: 170 °C/0.001 Torr.

In summary, the reaction of 4-amino-1-azabutadienes **1** with methyl acrylate and methacrylate offers an easy, high-yield route to 3,4-dihydro-2(1*H*)-pyridinones. The procedure has the advantages of ready availability of starting materials, ease of work-up, and simple purification of the reaction crude product.

Melting points were taken on samples in open capillary tubes in a Büchi melting point apparatus and are uncorrected. The NMR spectra were obtained on a Varian FT-80 NMR spectrometer. Microanalyses were performed on a Perkin-Elmer Model 240. Mass spectra were recorded on a Hewlett-Packard 5930A.

5-Imidoyl-3,4-dihydro-2(1*H*)-pyridinone Derivatives 3; General Procedure:

A solution of 4-amino-1-azabutadiene **1** (5 mmol) in dry THF (50 ml) is added under argon to a stirred suspension of KH (0.28 g, 7 mmol) in dry THF (15 mL) at 0°C and stirring is continued for 1 h. The acrylic ester (7 mmol) is then added dropwise. The mixture is allowed to warm to room temperature and stirred for 14 h. Anhydrous MeOH (10 mL) are carefully added, and then the solution is slowly poured into ice-cooled water and extracted with Et_2O (3 x 50 mL). The dried (Na_2SO_4) organic phase is evaporated, and the residue recrystallized (see Table 1).

5-Imidoyl-1-methyl-3,4-dihydro-2(1*H*)-pyridinone Derivatives 4; General Procedure:

A 1.5 M ethereal solution of *n*-butyllithium (4.6 mL, 7 mmol) is added under argon to a solution of **3** (5 mmol) in dry THF (60 mL) at 0°C, and stirring is continued for 1 h. Then CH_3I (0.44 mL, 7 mmol) is added dropwise. The solution is allowed to warm to room temperature, stirred for 14 h, and then slowly poured into ice-cooled water. The resultant mixture is extracted with Et_2O (3 x 50 mL), and the combined organic phase is dried (Na_2SO_4), filtered and evaporated. The residue is purified as reported in Table 1.

5-Acyl-3,4-dihydro-2(1*H*)-Pyridinone Derivatives 5; General Procedure:

A 1 M aq. H_2SO_4 solution (0.7 mL) is added to a solution of **3** (3 mmol) in THF (30 mL), and this solution is heated to 60°C for 4 h. The solution is poured into ice-cooled water, followed by extraction with Et_2O (3 x 50 mL). The dried (Na_2SO_4) organic phase is evaporated, and the residue recrystallized (see Table 2).

4,4-Diaroylbutanoic Acids 6; General Procedure:

Compounds **6** are synthesized by the method described for compounds **5** using 3 M aq. H_2SO_4 (10 mL) and stirring for 12 h (see Table 2).

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(1) Yates, F.S., in: *Comprehensive Heterocyclic Chemistry*, Vol. 2, Boulton, A.J., McKillop, A. (eds.), Pergamon Press, 1984, Chap. 2.09, p. 511.
Glasby, J.S., in: *Encyclopedia of the Alkaloids*, Plenum Press, New York, 1975.

(2) Jones, G., in: *Comprehensive Heterocyclic Chemistry*, Vol. 2, Boulton, A.J., McKillop, A. (eds.), Pergamon Press, 1984, Chap. 2.08, p. 395.

(3) Banerjee, D.K., Sengupta, P., Das Gupta, S.K. *J. Org. Chem.* **1954**, *19*, 1516.
Schumann, D., Naumann, A. *Liebigs Ann. Chem.* **1983**, 220.

(4) Komatsu, M., Yamamoto, S., Ohshiro, Y., Agawa, T. *Tetrahedron Lett.* **1981**, *22*, 3769.

(5) Sain, B., Baruah, J.N., Sandhu, J. *J. Chem. Soc. Perkin Trans. 1* **1985**, 773.

(6) Barluenga, J., Jardón, J., Rubio, V., Gotor, V. *J. Org. Chem.* **1983**, *48*, 1379.
Barluenga, J., Tomás, M., Ballesteros, A., Gotor, V., Krüger, C., Tsay, Y.H. *Angew. Chem.* **1986**, *98*, 190; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 181.

(7) Barluenga, J., Jardón, J., Gotor, V. *J. Org. Chem.* **1985**, *50*, 802.

(8) Hopkins, G.C., Jonak, J.P., Minnemeyer, H.J., Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040.